

Exhibit B

Sections 10-21, 16-6, 16-7, 16-8, and 16-56 from
Smith, M.B., and March, J. March's Advanced Organic Chemistry,
5th ed., Wiley (New York, N.Y., 2001)

10-19 *Alkylation With Onium Salts*

ALKOXY-DE-HYDROXYLATION

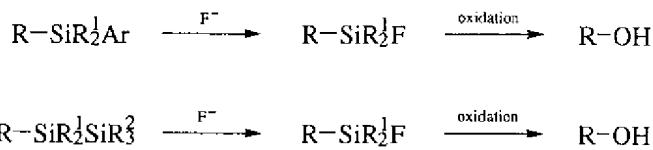


Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.⁶⁹⁶ Quaternary ammonium salts can sometimes also be used.⁶⁹⁷

OS VIII, 536.

10-20 *Hydroxylation of Silanes*

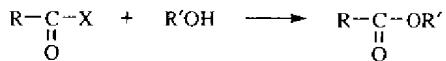
HYDROXY-DE-SILYLALKYLATION



Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This requires either an aryl group⁶⁹⁸ or another silyl group⁶⁹⁹ attached to silicon. Treatment with a fluorinating agent such as tetrabutylammonium fluoride or CsF replaces Ar or SiR₃ with F, which is oxidized with hydrogen peroxide or a peroxy acid to give the alcohol. This sequence is often called the *Tamao-Fleming oxidation*.⁶⁹⁸ There are several variations in substrate that allow versatility in the initial incorporation of the silyl unit.⁷⁰⁰

D. *Attack by OR at an Acyl Carbon*10-21 *Alcoholysis of Acyl Halides*

ALKOXY-DE-HALOGENATION



The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.⁷⁰¹ As with 10-8, the mechanism can be S_N1 or tetrahedral.⁵⁵⁹ Pyridine catalyzes the reaction by the nucleophilic catalysis route (see 10-9). The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten-Baumann procedure*, but pyridine is also frequently used. Both R and R' may be primary, secondary, or tertiary alkyl or aryl. Enolic esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R', the alkoxide can be used instead of the alcohol.⁷⁰² Activated alumina has also been used as a catalyst, for tertiary R'.⁷⁰³ Thallium salts of phenols give very high yields of phenolic esters.⁷⁰⁴ Phase-transfer catalysis has been used for hindered phenols.⁷⁰⁵ Zinc has been used to couple alcohols and acyl chlorides.⁷⁰⁶ Selective acylation is possible in some cases.⁷⁰⁷

When phosgene
is used.

An important exam-
ple is the use of
phosgene and
amino groups dur-
ing the synthesis of
Acyl halides re-
act with water to form
an ester.⁷⁰⁸

Acyl halides can
react with alcohols, in MeCN



This is a method
OS I, 12; III, 1
V, 1, 166, 168, 17

10-22 *Alcoholysis of Acyl Halides*

ALKOXY-DE-ACYLATION

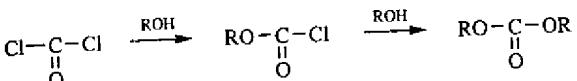


The scope of the
reaction is somewhat less re-
stricted. Acids, L
pyridine,⁷¹⁰ Cat-
Dimethylamino
where pyridine
TaCl₅-SiO₂,⁷¹³
acid can be pro-
duced. Cycli-

Alcohols can a-
cetate-phospho-
OS I, 285, 4
833; IV, 15, 2-
141, 258.

10

Reaction with phosphorus compounds. One of the most common reagents used with phosphorus compounds is the acyl halide, haloformic esters or carbonates can be prepared by reaction with phosphorus compounds.

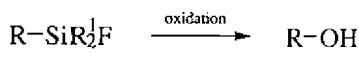
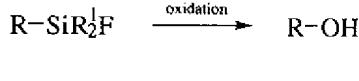


Acyl halides, and ethers can be conveniently prepared from phenols or phenols. ⁶⁹⁶ Quaternary ammonium

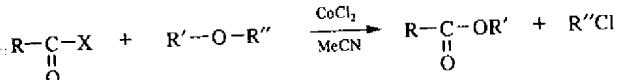
Important example is the preparation of carbobenzoxy chloride ($\text{PhCH}_2\text{OCOCl}$) from benzyl chloride and benzyl alcohol. This compound is widely used for protection of hydroxyl groups during peptide synthesis (see 10-55).

Acyl halides react with thiols, in the presence of zinc, to give the corresponding thioesters. ⁷⁰⁸

Acyl halides can also be converted to carboxylic acids by using ethers instead of phenols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride. ⁷⁰⁹



silyl unit converted to a hydroxy unit. The silyl group ⁶⁹⁹ attached to silicon. Treatment with trityl ammonium fluoride or CsF replaces the hydrogen peroxide or a peroxy acid to give the *Tamao-Fleming oxidation*. ⁶⁹⁸ The versatility in the initial incorporation



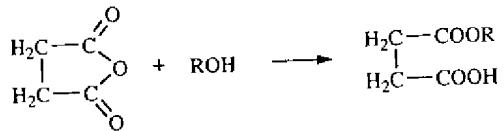
This is a method for the cleavage of ethers (see also 10-71). ⁷⁰⁹

10-22 Alcoholysis of Anhydrides

ALKOXY-DE-ACYLOXY-SUBSTITUTION



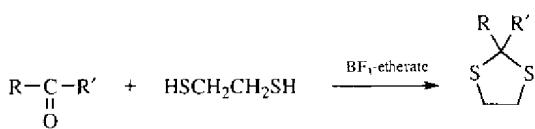
The scope of this reaction is similar to that of 10-21. Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare carboxylic acids. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine. ⁷¹⁰ Catalysis by pyridine is of the nucleophilic type (see 10-9). 4-(*N,N*-Dimethylamino)pyridine is a better catalyst than pyridine and can be used in cases where pyridine fails. ⁷¹¹ Nonbasic catalysts are cobalt(II) chloride ⁷¹² and $\text{NaCl}_5\text{-SiO}_2$. ⁷¹³ Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols ⁷¹⁴ or phenols ⁷¹⁵ with acetic-formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids, for example,



Alcohols can also be acylated by mixed organic-inorganic anhydrides, such as acetic-phosphoric anhydride, MeCOPO(OH)_2 (see 10-35). ⁷¹⁶

It is believed to proceed by a $\text{S}_{\text{N}}2$ mechanism. ⁵⁵⁹ Pyridine catalysis is also used. ⁷¹⁷ The reaction is often tetrahedral. ⁷¹⁸ A base is frequently added. ⁷¹⁹ Aqueous alkali is used, this is called the *Wolff-Kishner* route. ⁷²⁰ Pyridine is also frequently used. Both R and R' can be alkyl or aryl. Enolic esters can also be prepared. ⁷²¹ Enolates compete in these cases. In difficult cases, R' , the alkoxide can be used instead of the enolate. ⁷²² Zinc has been used as a catalyst, for tertiary R' . ⁷²³ Zinc has been used as a catalyst, for tertiary R' . ⁷²⁴ Zinc has been used as a catalyst, for tertiary R' . ⁷²⁵ Zinc has been used as a catalyst, for tertiary R' . ⁷²⁶ Zinc has been used as a catalyst, for tertiary R' . ⁷²⁷ Zinc has been used as a catalyst, for tertiary R' . ⁷²⁸ Zinc has been used as a catalyst, for tertiary R' . ⁷²⁹ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁰ Zinc has been used as a catalyst, for tertiary R' . ⁷³¹ Zinc has been used as a catalyst, for tertiary R' . ⁷³² Zinc has been used as a catalyst, for tertiary R' . ⁷³³ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁴ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁵ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁶ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁷ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁸ Zinc has been used as a catalyst, for tertiary R' . ⁷³⁹ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁰ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴¹ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴² Zinc has been used as a catalyst, for tertiary R' . ⁷⁴³ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁴ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁵ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁶ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁷ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁸ Zinc has been used as a catalyst, for tertiary R' . ⁷⁴⁹ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵⁰ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵¹ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵² Zinc has been used as a catalyst, for tertiary R' . ⁷⁵³ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵⁴ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵⁵ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵⁶ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵⁷ Zinc has been used as a catalyst, for tertiary R' . ⁷⁵⁸

acetals, are stable in the presence of bases, except that a strong base can remove the aldehyde proton, if there is one (see 10-107)⁸⁶. A common method for the protection of ketones involves treatment with ethanedithiol to give a cyclic dithioketal.⁸⁷ All subsequent reactions involving the R or R' group, the protecting group can then

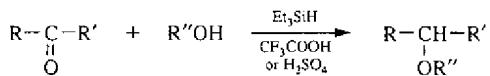


be removed by 10-6. Alternatively, the dithioketal can be desulfurized with Raney nickel (14-34), giving the overall conversion C=O → CH₂. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of TiCl₄,⁸⁸ SiCl₄,⁸⁹ with a disulfide (RSSR; R = alkyl or aryl),⁹⁰ or with methylthio(trimethylsilyl)ane (MeSSiMe₃).⁹¹

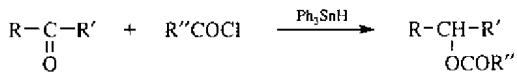
OS I, 1, 298, 364, 381; II, 137; III, 123, 387, 502, 536, 644, 731, 800; IV, 21, 479, 679; V, 5, 292, 303, 450, 539; VI, 567, 666, 954; VII, 59, 149, 168, 177, 241, 271, 297; VIII, 357. Also see OS IV, 558, 588; V, 25; VIII, 415.

16-6 Reductive Alkylation of Alcohols

C-HYDRO-O-ALKYL-ADDITION



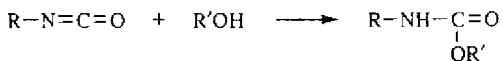
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid⁹² or by hydrogenation in alcoholic acid in the presence of platinum oxide.⁹³ The process can formally be regarded as addition of ROH to give a hemiacetal RR'C(OH)OR'', followed by reduction of the OH. In this respect, it is similar to 16-14. In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.⁹⁴



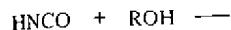
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone → dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.⁹⁵

16-7 The Addition of Alcohols to Isocyanates

N-HYDRO-C-ALKOXY-ADDITION



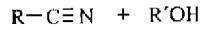
isocyanates (substituted urethanes). This is an excellent reaction. Formic acid HNCO gives unsaturated isocyanates, and CO gives *allophanates*.



urethanes are made by condensation of compounds containing two O atoms with isocyanates (RNHCOSR'),⁹⁶ though the mechanism is not clear. The details of the mechanism of the reaction of an isocyanate with an alcohol is certainly attacking the carbonyl carbon. This implicates the kinetic picture of the reaction catalyzed by metallic compounds such as TiCl₄ or SnCl₄⁹⁷ or n-butyllithium or LiAlH₄.⁹⁸ OS I, 140; V, 162; VI, 95,

16-8 Alcoholysis of Nitriles

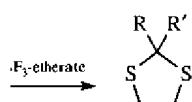
C-ALKOXY, OXO-DE-NITRILo-TER



The addition of dry HCl to a nitrile in a polar solvent leads to the hydrochlorides (imino esters and imino ethers). The imino esters can be converted to the free acid by treatment with sodium bicarbonate, or it can be converted to the corresponding carboxylic ester by treatment with aqueous NaOH. In the beginning, in which case aqueous NaOH is eliminated. Imino esters can be converted to the corresponding carboxylic ester by treatment with aqueous NaOH. This reaction is of broad application for the synthesis of macrocyclic R and for nitrile oxide formation. Application of the reaction to the synthesis of macrocyclic R and for nitrile oxide formation is a method for the synthesis of macrocyclic R and for nitrile oxide formation. Cyanogen chloride reacts with HCl or AlCl₃ to give carboxylic acids.

The alcohol ROH can also be added to OS I, 5, 270; II, 284, 310.

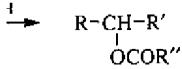
that a strong base can remove the common method for the protection to give a cyclic dithioketal.⁸⁷ After this, the protecting group can then



al can be desulfurized with Raney
 $\text{Ni} \rightarrow \text{CH}_2$. Dithioacetals can also be
 reacted with thiols in the presence of a
 alkyl or aryl),⁹⁰ or with methylthio-

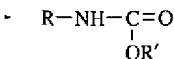
32, 536, 644, 731, 800; IV, 21, 479;
VII, 59, 149, 168, 177, 241, 271;
; VIII, 415.

s by treatment with an alcohol and by hydrogenation in alcoholic acid. This can formally be regarded as OR' , followed by reduction of the C=O group. In a similar reaction, ketones can be converted (into aldehydes or alcohols) by treatment with an alcohol and

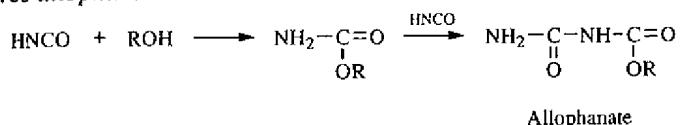


e dimerization of two molecules of dicyclohexyl ether). This was a trialkylsilane and a catalyst.⁹⁵

tes



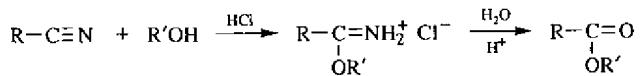
Carbamates (substituted urethanes) are prepared when isocyanates are treated with carboxylic acids. This is an excellent reaction, of wide scope, and gives good yields. Reaction of isocyanic acid HNCO gives unsubstituted carbamates. Addition of a second mole of CO_2 gives *allophanates*.



urethanes are made by combining compounds with two NCO groups with compounds containing two OH groups. Isothiocyanates similarly give thiocarbonates ($\text{RNHCOSR}'$),⁹⁶ though they react slower than the corresponding isocyanates. The details of the mechanism are poorly understood,⁹⁷ though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding implicates the kinetic picture.⁹⁸ The addition of ROH to isocyanates can also be catalyzed by metallic compounds,⁹⁹ by light,¹⁰⁰ or, for tertiary ROH, by lithium oxides¹⁰¹ or *n*-butyllithium.¹⁰²

8. *Alcoholysis of Nitriles*

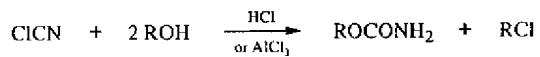
KOXY, OXO-DE-NITRILo-TERSUbSTITUTION



The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.¹⁰³ The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.¹⁰⁴

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group identified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst such as HCl or AlCl₃ to give carbamates:¹⁰⁵



The alcohol ROH can also be added to nitriles in another manner (16-56). **OS I**, 5, 270; **II**, 284, 310; **IV**, 645; **VI**, 507; **VIII**, 415.

by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means products can be obtained from aldehydes that normally fail to self-condense.⁸⁶⁰

OS I, 94; VII, 95.

16-55 Addition of Radicals to C=O, C=S, C=N Compounds

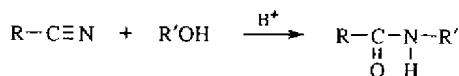
Radical cyclization is not limited to a radical attacking a C=C unit (see 15-35 and 15-36), and reactions with both C=N and C=O moieties are known. Reaction of MeON=CH(CH₂)₃CHO with Bu₃SnH and AIBN, for example led to *trans*-*z*-(methoxyamino)cyclopentanol in good yield.⁸⁶¹ Addition of radical to the C=N unit of R-C=N-SPh⁸⁶² or R-C=N-OBz⁸⁶³ led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.⁸⁶⁴ Radical also add to the carbonyl unit of phenylthio esters to give cyclic ketones.⁸⁶⁵

Reactions in Which Carbon Adds to the Hetero Atom

A. Oxygen Adding to the Carbon

16-56 The Ritter Reaction

N-HYDRO,N-ALKYL-C-OXO-BIADDITION

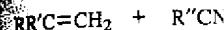


Alcohols can be added to nitriles in an entirely different manner from that of Reaction 16-8. In this reaction, the alcohol is converted by a strong acid to a carbocation, which adds to the negative nitrogen, water adding to the carbon:



The immediate product tautomerizes to the N-alkyl amide. Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.⁸⁶⁶ Hydrogen cyanide also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.⁸⁶⁷ Since the amides (especially the formamides) are easily hydrolyzable to amines, the Ritter reaction provides a method for achieving the conversions R'OH → R'NH₂ (see 10-46) and alkene → R'NH₂ (see 15-8) in those cases where R' can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by

ment with triflic anhydride in the presence of the nitrile. Alkenes of the form R-CH=CH₂ react with mercuric nitrate to give the corresponding acids.



The Ritter reaction (NHCONHR').⁸⁷¹ OS V, 73, 471.

16-57 Acylation of Aldehydes

ACYL-C-ACYLOXY-ADDITION

Aldehydes can be converted to acyl aldehydes in the presence of BF₃, other reagents cannot normally be applied. The reagent is trichloroacetyl isopropylidene catalyst.⁸⁷⁵

OS IV, 489.

16-58 The Addition of

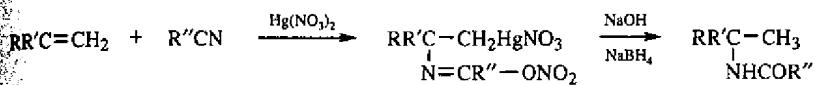
When catalyzed by acids, cyclic acetals, the most common being formaldehyde is called *paraldehyde*. Under certain conditions, aldehydes can also polymerize. It is required to form hemiacetals, formed from formaldehyde. Because formaldehyde is so convenient to use, there

components in a phase-transfer agent with triflic anhydride⁸⁶⁸ or $\text{Ph}_2\text{CCl}^+ \text{SbCl}_6^-$ or a similar salt⁸⁶⁹ in the presence of the nitrile.

Alkenes of the form $\text{RCH}=\text{CHR}'$ and $\text{RR}'\text{C}=\text{CH}_2$ add to nitriles in the presence of mercuric nitrate to give, after treatment with NaBH_4 , the same amides that would be obtained by the Ritter reaction.⁸⁷⁰ This method has the advantage of avoiding strong acids.

$=N$ Compounds

ing a $\text{C}=\text{C}$ unit (see 15-35 and 15-36) and $\text{C}=\text{N}$ units are known. Reaction of $\text{C}=\text{C}$ with $\text{R}'\text{C}=\text{CH}_2$ for example led to *trans*-addition of radical to the $\text{C}=\text{N}$ unit to give imines. Radical addition to $\text{C}=\text{C}$ also add to the carbonyl unit.

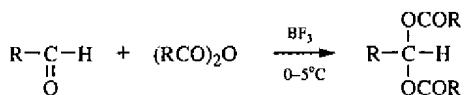


The Ritter reaction can be applied to cyanamides RNHCN to give ureas (RNHCOR').⁸⁷¹ OS V, 73, 471.

16-57 Acylation of Aldehydes and Ketones

tert Atom

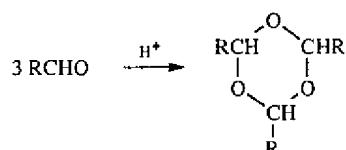
α -ACYL-C-ACYOXY-ADDITION



Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of BF_3 , other Lewis acids,⁸⁷² proton acids,⁸⁷³ or PCl_3 .⁸⁷⁴ The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.⁸⁷⁵

OS IV, 489.

16-58 The Addition of Aldehydes to Aldehydes



When catalyzed by acids, low molecular weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.⁸⁷⁶ The cyclic trimer of formaldehyde is called *trioxane*,⁸⁷⁷ and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers⁸⁷⁸ or dimers. Aldehydes can also polymerize to linear polymers, but here a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.